Original Article

Complications related to extracorporeal life support in lung transplantation: single-center analysis※

Michaela Orlitová[1,2], Wout Goos[2], Jan Van Slambrouck[1,3], Karlien Degezelle[4], Cedric Vanluyten[1,3], Christelle Vandervelde[1,3], Julie De Beule[1], Xin Jin[1,3], Evelien Berkmans[1,3], Paul De Leyn[1,3], Herbert Decaluwé[1,3], Hans Van Veer[1,3], Lieven Depypere[1,3], Geert M. Verleden[3,5], Laurent Godinas[3,5], Robin Vos[3,5], Erwin De Troy[6,7], Dieter F. Dauwe[6,7], Catherine Ingels[6,7], Philippe Meersseman[8], Greet Hermans[7,8], Joost Wauters[8,9], Filip Rega[2,10], Bart Meyns[2,10], Tom Verbelen[2,10], Dirk E. Van Raemdonck[1,3], Arne P. Neyrinck[2,11], Laurens J. Ceulemans[1,3]^

[1]Department of Thoracic Surgery, University Hospitals Leuven, Leuven, Belgium; [2]Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium; [3]Department of Chronic Diseases and Metabolism, Laboratory of Respiratory Diseases and Thoracic Surgery (BREATHE), KU Leuven, Leuven, Belgium; [4]Division of Perfusion, Department of Cardiac Surgery, University Hospitals Leuven, Leuven, Belgium; [5]Department of Respiratory Diseases, University Hospitals Leuven, Leuven, Belgium; [6]Department of Intensive Care Medicine, University Hospitals Leuven, Leuven, Belgium; [7]Department of Cellular and Molecular Medicine, Laboratory of Intensive Care Medicine, KU Leuven, Leuven, Belgium; [8]Department of General Internal Medicine, Medical Intensive Care Unit, University Hospitals Leuven, Leuven, Belgium; [9]Department of Microbiology, Immunology and Transplantation, Laboratory for Clinical Infectious and Inflammatory Disorders, KU Leuven, Leuven, Belgium; [10]Department of Cardiac Surgery, University Hospitals Leuven, Leuven, Belgium; [11]Department of Anesthesiology and Algology, University Hospitals Leuven, Leuven, Belgium

Contributions: (I) Conception and design: M Orlitová, R Vos, E De Troy, DF Dauwe, T Verbelen, DE Van Raemdonck, AP Neyrinck, LJ Ceulemans; (II) Administrative support: J Van Slambrouck, K Degezelle; (III) Provision of study materials or patients: P De Leyn, H Decaluwé, H Van Veer, L Depypere, GM Verleden, L Godinas, R Vos, E De Troy, DF Dauwe, C Ingels, P Meersseman, G Hermans, J Wauters, F Rega, B Meyns, T Verbelen, DE Van Raemdonck, AP Neyrinck, LJ Ceulemans; (IV) Collection and assembly of data: M Orlitová, W Goos, J Van Slambrouck, K Degezelle, C Vanluyten, C Vandervelde, J Debeule, X Jin; (V) Data analysis and interpretation: M Orlitová, W Goos, J Van Slambrouck, R Vos, T Verbelen, DE Van Raemdonck, AP Neyrinck, LJ Ceulemans, E Berkmans; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Prof. Dr. Laurens J. Ceulemans, MD, PhD. Department of Thoracic Surgery and Lung Transplantation, University Hospitals Leuven/KU Leuven, Herestraat 49, 3000 Leuven, Belgium; Department of Thoracic Surgery, University Hospitals Leuven, Leuven, Belgium; Department of Chronic Diseases and Metabolism, Laboratory of Respiratory Diseases and Thoracic Surgery (BREATHE), KU Leuven, Leuven, Belgium. Email: laurens.ceulemans@uzleuven.be.

Background: Extracorporeal life support (ECLS) is not routinely used at our center during sequential single-lung transplantation (LTx), but is restricted to anticipate and overcome hemodynamic and respiratory problems occurring peri-operatively. In this retrospective descriptive cohort study, we aim to describe our single-center experience with ECLS in LTx, analyzing ECLS-related complications.

Methods: All transplantations with peri-operative ECLS use [2010–2020] were retrospectively analyzed. Multi-organ and heart-lung transplantation were excluded. Demographics, support type and indications are described. Complications are categorized according to the underlying nature and type. Data are presented as median [interquartile range (IQR)]. Kaplan-Meier was used for survival analysis.

Results: The overall use of ECLS was 22% (156/703 patients) with a mean age of 52 years (IQR, 36–59 years). Transplant indications in ECLS cohort were interstitial lung disease (38%; n=60), chronic obstructive pulmonary disease (COPD) (19%; n=29), cystic fibrosis (17%; n=26) and others (26%; n=41). Per indication, 94% (15/16) of pulmonary arterial hypertension patients required ECLS, whereas only 8% (29/382) of COPD patients did. In 16% (25/156) of supported patients, veno-venous extracorporeal membrane oxygenation was initiated, while 77% (120/156) required veno-arterial support, and 7% (11/156) cardiopulmonary bypass. Thirty-day mortality was 6% (9/156). Sixteen percent (25/156) of patients were

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^ ORCID: 0000-0002-4261-7100.

bridged to transplantation on ECLS and 24% (37/156) required post-operative support. Main reasons to use ECLS were intra-operative hemodynamic instability (53%; n=82), ventilation/oxygenation problems (22%; n=34) and reperfusion edema (17%; n=26). Overall incidence of patients with at least one ECLS-related complication was 67% (n=104). Most common complications were hemothorax (25%; n=39), need for continuous renal replacement therapy (19%; n=30), and thromboembolism (14%; n=22).

Conclusions: ECLS was required in 22% of LTxs, with a reported ECLS-related complication rate of 67%, of which the most common was hemothorax. Larger databases are needed to further analyze complications and develop tailored deployment strategies for ECLS-use in LTx.

Keywords: Complications; extracorporeal life support (ECLS); lung transplantation (LTx)

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Introduction

Lung transplantation (LTx) remains the only therapeutic option for patients with end-stage lung disease. Although the overall survival after LTx has improved over the years, the surgical procedure and post-LTx patient care remain challenging (1). Extracorporeal life support (ECLS) is often used to overcome the challenges like acute pre-transplant recipient deterioration, primary graft dysfunction (PGD) or other intra- and post-procedural events (2,3). Although encouraging results have been reported for patients bridged with ECLS to LTx (4-7) or for extended post-procedural ECLS of pulmonary arterial hypertension (PAH) patients (8-10), the routine use of intra-operative ECLS remains a matter of debate. In the past years the superiority of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) over cardiopulmonary bypass (CPB) has been shown (11-13). Intra-operative ECLS use ranges from 27–100% in different large-volume centers, depending on the choice of strategy between ECLS use-on-indication ("off-pump") or routine use (14-16). Although a recent consensus document from The American Association of Thoracic Surgery provides recommendations about intra-operative ECLS use, there is still no international consensus in favor of either off-pump or routine ECLS strategy (17). ECLS is an essential part of every LTx program, however, its invasive nature might be a source of complications, as previously reported (14,15).

The aim of this study is to retrospectively analyze our experience with ECLS within our LTx program where an off-pump LTx strategy is used, as well as to describe the incidence and nature of ECLS-related complications. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-443/rc).

Highlight box

Key findings

- In a high-volume lung transplantation (LTx) center with an off-pump intra-operative extracorporeal life support (ECLS) strategy, ECLS is used in 22% of LTx cases of which 67% develop an ECLS-related complication.

What is known and what is new?

- ECLS is an essential part of every LTx program, however, the local practices of its use differ substantially among various large volume LTx centers.
- We provide a meticulous description of ECLS-related complications and report that not all LTx indications require the same need for intra-operative ECLS.

What is the implication, and what should change now?

- Since the majority of LTx procedures can be performed without ECLS, and ECLS comes with an unavoidable complication risk, its use should be carefully considered case-by-case. Further prospective studies are needed to achieve an international consensus on the use of ECLS during LTx.

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). There is no experiment in this paper as it is a retrospective study of clinical strategies, therefore informed consent is not

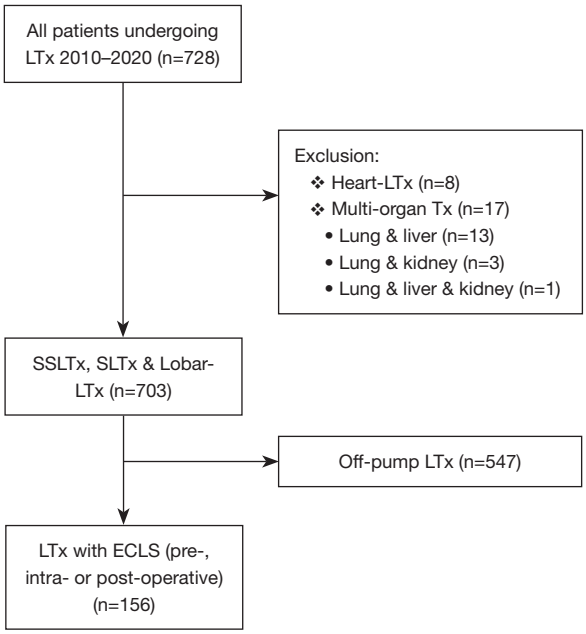


Figure 1 Flowchart of patient selection. Combined heart-lung and multiorgan Tx patients were excluded (n=25). One hundred fifty-six ECLS LTx cases were identified for the final analysis. LTx, lung transplantation; Tx, transplantation; SSLTx, sequential single LTx; SLTx, single LTx; ECLS, extracorporeal life support.

required. The study was approved by the local ethics committee (No. S64384/S51577).

Study design and patient selection

A retrospective single-center descriptive cohort study of patients undergoing LTx with ECLS at University Hospitals Leuven, Belgium was performed. All patients undergoing LTx in our center between January 1st, 2010 until December 31st, 2020 were assessed (n=728; *Figure 1*). Patients undergoing heart-LTx (n=8) or multi-organ transplantation (n=17) were excluded. Within the remaining cohort (n=703), those undergoing LTx with ECLS at any peri-operative timepoint were identified and included in the final analysis (n=156). To avoid patient selection bias, a descriptive analysis of the entire ECLS cohort was performed. In the off-pump cohort (n=547), only survival was assessed. Patients were followed-up until September 15th, 2022. Data were collected from electronic patient files.

ECLS strategy

At our center the standard procedure is to perform off-pump sequential single-LTx (SSLTx) through bilateral anterior thoracotomy. ECLS is used to anticipate and overcome hemodynamic and/or oxygenation problems occurring pre-, intra- or post-operatively. At the multidisciplinary pre-transplant meeting an ECLS strategy for each patient is discussed. Hilar test clamping is performed intra-operatively to assess need for ECLS and to avoid ECLS initiation in an acute setting. A decision to start ECLS is based on a case-by-case clinical assessment of hemodynamic and oxygenation parameters and gas exchange. Cannulation and initiation of ECLS is routinely performed by a member of the cardiac surgical team. In case of veno-venous (VV) or VA-ECMO, 100 IU/kg of unfractionated heparin is administered. CPB is reserved for major bleeding complications and concomitant cardiac procedures, increasing the heparin dose to 300–400 IU/kg.

ECLS cohort

Demographic data of donors and recipients were reviewed, as well as recipient variables that could influence the use of ECLS: transplant indication, high urgency status, previous thoracic surgery, pre-operative intensive care unit (ICU)-stay and mechanical ventilation. Reasons for ECLS initiation as well as ECLS characteristics including type, cannulation strategy and timing were analyzed and divided into groups with patients receiving ECLS as a bridge to LTx, intra- or post-operative support. In order to avoid listing of the same patient in several groups, the moment of ECLS initiation determined the group. If a patient received more than one type of ECLS support, only the most invasive one was considered (from least to most invasive: VV-ECMO < VA-ECMO < CPB).

Reflecting the post-procedural coagulation capacity, we analyzed international normalized ratio and thrombocytes level at admission to ICU and fluid balance. Regarding the short- and long-term outcomes in our ECLS cohort, we analyzed PGD grades (PGD-3) and incidence, length of ICU and hospital stay, 30- and 90-day mortality, incidence of chronic lung allograft dysfunction (CLAD), and 1-/5-year patient survival. PGD was graded according to the 2016 International Society for Heart and Lung Transplantation (ISHLT) consensus definition (18). CLAD

Table 1 Definition of ECLS-related complications

Complication	Definition
Direct relation to ECLS	
Vascular	Vessel perforation, pseudoaneurysm, dissection, air embolism, limb compartment syndrome, limb ischemia
Wound cannulation site	Wound complications associated with cannulation and requiring VAC therapy or surgical intervention
Mechanical	Clots in the circuit, oxygenator failure, cannula thrombus
Indirect relation to ECLS	Definition
Hemothorax	Need for revision
Thromboembolism	Systemic thromboembolism, deep venous thrombosis
Neurological	Ischemic or bleeding CVA
Acute kidney injury	Decrease of renal function requiring CRRT

ECLS, extracorporeal life support; VAC, vacuum-assisted closure therapy; CVA, cerebrovascular accident; CRRT, continuous renal replacement therapy.

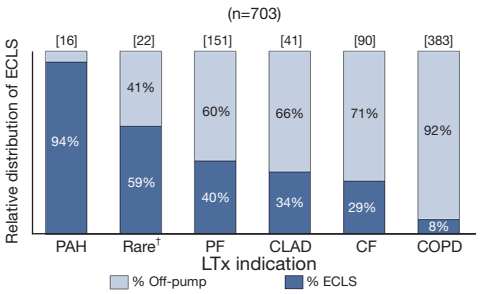


Figure 2 ECLS use by indication for LTx shows a broad distribution of ECLS need according to different LTx indications. †, pulmonary veno-occlusive disease (n=2), IgG3 deficiency (n=1), lymphangioleiomyomatosis (n=2), primary ciliary dyskinesia (n=1), alveolar proteinosis (n=2), Eisenmenger syndrome (n=2), chronic thromboembolic pulmonary hypertension (n=2) and Osler-Weber-Rendu disease (n=1). % Off-pump: ECLS was not used; % ECLS: ECLS was used. ECLS, extracorporeal life support; PAH, pulmonary arterial hypertension; PF, pulmonary fibrosis; CLAD, chronic lung allograft dysfunction; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; LTx, lung transplantation.

was also determined following ISHLT definition (19). Survival was compared between patients who did and did not develop an ECLS-related complication and between patients undergoing LTx with and without ECLS. According to Leuven LTx program policy, all patients are followed-up in our center, therefore no patients were lost to follow-up.

To clarify the context of our findings, we compared our series with three large volume centers that recently published their ECLS experience in LTx (8,14,20).

ECLS-related complications

ECLS-related complications were defined prior to data collection and divided according to their direct or indirect relation to ECLS (21). As summarized and defined in *Table 1*, directly related are vascular complications (22-24), wound complications (25-27) and mechanical complications related to ECLS circuit and components (28,29). Indirectly related are bleeding and thromboembolic events (26,30), neurological complications (31,32) and presence of acute kidney injury (33,34).

Statistics

Continuous variables were expressed as median [interquartile range (IQR)], categorical variables as absolute numbers and frequencies (%). GraphPad Prism 9 (GraphPad Software, San Diego, CA, USA) was used for statistical analysis. Kaplan-Meier analysis was used to assess patient survival (Log-rank test). Fisher's exact text was used for comparison of demographic data between our series and other studies. $P<0.05$ was considered significant. Missing data were reported, no statistical analysis was performed.

Results

One hundred and fifty-six (22%) patients transplanted between 2010–2020 required intra-operative ECLS. The LTx indications with the highest incidence of ECLS were PAH, rare diseases and pulmonary fibrosis (PF) (*Figure 2*).

Pre- and post-transplant donor and recipient characteristics are summarized in *Table 2*. Lungs were

Table 2 Donor and ECLS cohort characteristics

Characteristics	Values (N=156)
Donor characteristics	
National donor	107 [69]
International donor (Eurotransplant)	46 [29]
International donor (non-Eurotransplant)	3 [2]
DBD	124 [79]
DCD	32 [21]
Female	65 [42]
Age (years)	49 [40–58]
Weight (kg)	75 [66–83]
Height (cm)	175 [165–180]
BMI (kg/m^2)	24.5 [22.8–26.3]
Smoking history	55 [35]
Length of ventilation (hours)	62 [38–120]
CMV mismatch (D+, R–)	37 [24]
Pre-operative recipient characteristics	
Female	78 [50]
Age (years)	52 [36–59]
Weight (kg)	64 [53–78.25]
Height (cm)	169 [160–176]
BMI (kg/m^2)	22.1 [19.3–26.3]
BSA (m^2)	1.72 [1.58–1.93]
Indication to LTx	
Pulmonary fibrosis	60 [38]
COPD	29 [19]
Cystic fibrosis	26 [17]
Pulmonary arterial hypertension	15 [10]
Other disorders	12 [8]
CLAD-BOS	12 [8]
CLAD-RAS	2 [1]
Previous surgery	53 [34]
Thoracic	48 [31]
Cardiac	5 [3]
Surgical access (previous surgery)	
Open thoracotomy	18 [12]
Video-assisted thoracoscopy	17 [11]
Sternotomy	15 [10]
Endovascular cardiac procedure	2 [1]
Pre-operatively measured PAP	
US measured	92 [59]
Systolic PAP (mmHg)	54 [39.3–83.5]
RHC measured	64 [41]
Systolic PAP (mmHg)	52 [38–76]
Diastolic PAP (mmHg)	22 [15–35]
Mean PAP (mmHg)	32.5 [24–46.25]
Missing values	46 [29]
Pre-operative status	
High urgency status	33 [21]
Pre-operative ICU stay	40 [26]
Pre-operative ICU stay (days)	10 [6.75–16.25]
Pre-operative mechanical ventilation	22 [14]
Pre-operative mechanical ventilation (days)	8 [5.5–15.5]
Post-operative parameters & short-term outcome	
Any PGD grade 3 during 72 hours[†]	72 [46]
PGD grade 3 at 72 hours	35 [22]
INR at ICU admission	1 [1–1.1]
Thrombocytes at ICU admission (10^9 cells/L)	51.4 [35.25–74.75]
Positive total fluid balance in first 72 hours	124 [79]
Negative total fluid balance in first 72 hours	32 [21]
Length of ICU stay (days)	10.5 [6–27]
Length of hospital stay (days)	36 [25–57]
30-day mortality	9 [6]
90-day mortality[‡]	13 [8]
Long-term outcome	
CLAD incidence	37 [24]
CLAD-free survival (days)	919 [512–2,159]
1-year proportional survival (%)	83
5-year proportional survival (%)[§]	67

Values expressed as median [IQR] or N [%]. [†], 6/156 (4%) of patients were categorized as ungradable, and 5/156 (3%) died; [‡], reason of death: massive hemorrhage intra-operative (n=2), multiorgan failure (n=3), unsuccessful reanimation after cardiac arrest (n=3), respiratory failure and sepsis (n=2), fatal brain hemorrhage (n=1), pulmonary necrosis (n=1), pulmonary adenocarcinoma in the donor lung (n=1); [§], 32 patients were censored, 5-year survival not yet reached. ECLS, extracorporeal life support; DBD, donation after brain death; DCD, donation after circulatory death; BMI, body mass index; CMV, cytomegalovirus; D+, seropositive donor; R–, seronegative recipient; BSA, body surface area; LTx, lung transplantation; COPD, chronic obstructive pulmonary disease; CLAD-BOS, chronic lung allograft dysfunction-bronchiolitis obliterans syndrome; CLAD-RAS, chronic lung allograft dysfunction-restrictive allograft syndrome; PAP, pulmonary artery pressure; US, ultrasound; RHC, right heart catheterization; ICU, intensive care unit; PGD, primary graft dysfunction; INR, international normalized ratio; IQR, interquartile range.

procured following donation after brain-death in 124/156 (79%) cases. Median donor age was 49 years and 65/156 (42%) were female. Regarding recipients, median age was 52 years and 78/156 (50%) were female. One third of ECLS patients had a history of thoracic surgery, mostly performed through open thoracotomy. The median pre-operative systolic pulmonary artery pressure for patients measured with ultrasound (n=92) was 54 mmHg and for patients measured with right heart catheterization (n=64) mean pulmonary artery pressure was 32.5 mmHg. Twenty-six percent of ECLS-patients were hospitalized in ICU pre-LTx.

Post-operatively, PGD-3 within 72 hours occurred in 72/156 (47%) of patients and 35/156 (22%) were graded PGD-3 at 72 hours post-LTx. Ninety-day mortality was 13/156 (8%) including 2 patients who died during surgery. CLAD developed in 37/156 (24%) of patients. One- and 5-year patient survival were 83% and 67%, respectively. Median follow-up post-LTx was 4.5 (IQR, 1.8–8.5) years.

ECLS initiation and duration

LTx procedure and ECLS-related characteristics are summarized in *Table 3*. Total ischemic time of right and left lung were 431 (IQR, 346–510) and 502 (IQR, 353–601) minutes, respectively. Median anastomosis time was 75 (IQR, 62–88) minutes per lung.

ECLS as bridge to transplant

Median duration of ECLS as bridge to LTx (n=25) was 7 (IQR, 5.5–10.2) days. The most common LTx indication in bridged patients was cystic fibrosis in 10/25 (40%), followed by PF 8/25 (32%) and redo-transplant for CLAD 4/25 (16%). All bridged patients were cannulated peripherally and 22/25 (88%) received VV-ECMO. In all cases ECLS was continued intra-operatively, although in 5/25 (20%) the mode of support changed during LTx, with 3/25 (12%) converted from VV- to VA-ECMO, 1/25 (4%) from VV-ECMO to CPB and 1/25 (4%) from VA-ECMO to CPB. Furthermore, in 7/25 (28%) ECLS was prolonged post-operatively.

Intra-operative ECLS

From patients where ECLS was initiated intra-operatively (n=130), 30/130 (23%) were a-priory-planned mostly patients with PAH (13/30; 43%) and PF (9/30; 30%). In 53/130 (41%) clamshell thoracotomy was performed. Most common indication for intra-operative ECLS was hemodynamic instability in 80/130 (62%). VA-ECMO was started in 112/130 (86%), mostly by central cannulation in 104/130 (80%). Analysis of the exact timing of intra-operative ECLS initiation (*Table 4*) revealed that in 12/130 (9%) cases, ECLS was initiated at a point during surgery after test clamping and pneumonectomy. Notably, in 6/12 (50%) of these cases, ECLS was initiated for surgical complications with bleeding, mostly atrial tear. In the other half of the cases, respiratory or hemodynamic deterioration developed. In 8/12 (67%) cases a conversion from bilateral anterior thoracotomy to clamshell was performed. Median duration of intra-operative ECLS was 302 (IQR, 179–405) minutes.

ECLS post-operative

Post-operative ECLS prolongation was required in 36/130 (28%) cases with a median duration of 2 (IQR, 1–3) days. Only one patient required ECLS post-operatively while transplantation was performed without ECLS. This was due to development of severe PGD.

ECLS-related complications

Annual distribution of different ECLS types and complication rate are illustrated in *Figure 3*. At least one complication was present in 104/156 (67%) of ECLS cases. The incidence of complications per group and per ECLS mode are plotted in *Figure 4A*,*4B*, respectively.

Complications directly related to ECLS occurred in 30/156 (19%) of patients, whereas 87/156 (56%) suffered from indirectly-related complications. In 13/156 (8%) of patients, more than one complication occurred.

Hemothorax requiring surgical revision was the most common complication and occurred mainly in patients with CPB, namely in 5/11 (45%). From the 30 patients requiring continuous renal replacement therapy (CRRT) post-transplant, 6 (20%) suffered from chronic kidney disease prior to LTx and in 13 (43%) ECLS was initiated due to intra-operative hemodynamic instability. Thromboembolism was mostly prevalent in the VV-ECMO group occurring in 6/29 (21%). Vascular complications consisted of air embolus in 4/11 (36%) patients, tear or other mechanical injury in the cannulated vessel in 3/11 (27%), leg compartment syndrome in 2/11 (18%) and leg ischemia in 2/11 (18%). These complications occurred mostly when the arterial circulation was cannulated. From ten patients with cannulation-site related wound complications, 7/10 (70%) developed hematoma requiring surgical intervention and 3/10 (30%) needed a vacuum-assisted therapy. Wound complications occurred mostly in the VV-ECMO group. The most common mechanical

Table 3 Procedure and ECLS-related characteristics

Variables	Bridge to LTx (n=25)	Intra-operative ECLS (n=130)	Post-operative ECLS (n=1)	Total (n=156)
LTx procedure				
LTx type: SL	0	4 [3]	0	4 [3]
LTx type: SSL	24 [96]	117 [90]	1 [100]	142 [91]
LTx type: lobar	1 [4]	9 [7]	0	10 [6]
Thoracotomy				
Anterior	21 [84]	77 [59]	1 [100]	99 [63]
Clamshell	4 [16]	53 [41]	0	57 [37]
EVLP use	0	5 [4]	0	5 [3]
Total ischemic time RL (min)	392 [357–518]	448 [343–509]	278	431 [346–510]
Total ischemic time LL (min)	551 [479–617]	484 [340–601]	512	502 [353–601]
Anastomosis time RL (min)	86 [74–92]	74 [62–87]	74	75 [64–88]
Anastomosis time LL (min)	77 [70–94]	74 [61–85]	88	75 [62–87]
Bridge to LTx				
Awake	11 [44]			11 [7]
Sedated	14 [56]			14 [9]
ECLS planned	0	30 [23]	0	30 [19]
ECLS indication				
Ventilatory or oxygenation problems	23 [92]	35 [27]	1 [100]	59 [38]
Hemodynamic Instability	2 [8]	80 [62]	0	82 [53]
Surgical complication	0	12 [9]	0	12 [8]
Other	0	3 [2]	0	3 [2]
ECLS type				
CPB	0	11 [8]	0	11 [6]
VA-ECMO	1 [4]	112 [86]	0	113 [72]
VV-ECMO	22 [88]	6 [5]	1 [100]	29 [19]
VVA-ECMO	2 [8]	1 [1]	0	3 [2]
ECLS cannulation				
Central	0	104 [80]	0	104 [67]
Peripheral	25 [100]	21 [16]	1 [100]	47 [30]
Combination	0	1 [1]	0	1 [1]
Missing values	0	4 [3]	0	4 [3]
Leg cannula	0	4 [3]	0	4 [3]

Values expressed as median [IQR] or N [%]. ECLS, extracorporeal life support; LTx, lung transplantation; SL, Single lung; SSL, sequential single lung; EVLP, ex-vivo lung perfusion; RL, right lung; LL, left lung; CPB, cardiopulmonary bypass; VA, veno-arterial; VV, veno-venous; VVA, veno-veno-arterial; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range.

Table 4 Detailed description of intra-operative ECLS initiation timing

Timepoint of ECLS initiation	Total (n=130), N [%]
Before induction (awake) in OR	4 [3]
After induction or immediately after thoracotomy	30 [23]
Before first pneumonectomy (proof-clamp)	43 [33]
After first pneumonectomy/during first implantation	6 [5]
Before second pneumectomy (proof-clamp)	39 [30]
After second pneumectomy/during second implantation	6 [5]
After second implantation	2 [2]

ECLS, extracorporeal life support; OR, operating room.

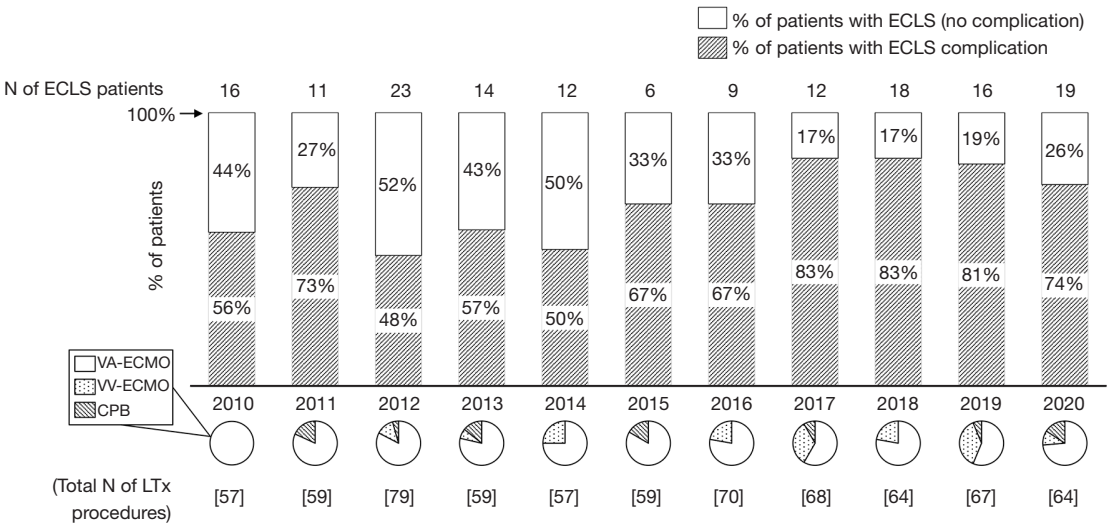


Figure 3 ECLS use and incidence of complications per year. Figure depicts detailed description of ECLS cases per year: incidence of complications (%) and modes of ECLS used. N, number; ECLS, extracorporeal life support; VA, veno-arterial; VV, veno-venous; ECMO, extracorporeal membrane oxygenation; CPB, cardiopulmonary bypass; LTx, lung transplantation.

complication was presence of clots in the circuit in 4/9 (44%) and cannula thrombus in 3/9 (3%) patients. Neurological complications presented as cerebrovascular bleeding in three patients (CPB or VA-ECMO). On average, patients supported with CPB developed 1.9 complications/case, patients on VV-ECMO 0.76 and VA-ECMO 0.64.

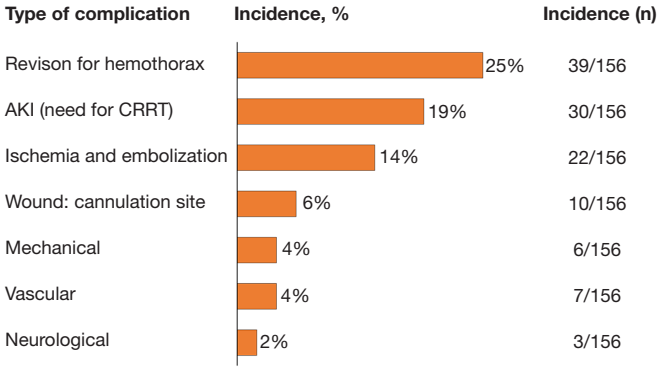
Survival analysis

Survival analysis of ECLS patients with *vs.* without complication (*Figure 5A*) revealed a significant difference at 1-year (P=0.0453) but comparable 5-year survival (P=0.4897). One- and 5-year patient survival was significantly better in the off-pump compared to ECLS cohort (P<0.0001 and P=0.0003; respectively) (*Figure 5B*). Median follow-up (off-pump and ECLS cohort) was 5.7 (IQR, 3.1–8.6) years.

Study comparison: patient inclusion criteria and demographic data

Patient inclusion criteria of three recently reported high volume LTx centers (8,14,20) are summarized in *Table 5*. Whereas two studies also included data from pre-, intra- and post-operative ECLS (14,20), our series is the only describing all modes of extracorporeal support, including

A



B

	CPB (n=11)	VV-ECMO (n=29)	VA-ECMO (n=116)
Revision for hemothorax	45%	21%	24%
AKI (need for CRRT)	64%	14%	16%
Thromboembolism	18%	21%	6%
Wound: cannulation site	9%	10%	5%
Mechanical	27%	7%	3%
Vascular	9%	3%	8%
Neurological	18%	0%	1%
Complication/patient (avg)	1.91	0.76	0.64

Figure 4 Incidence of ECLS-related complications. (A) Overall incidence per type of complication (for definition see *Table 1*). (B) Incidence of complications per mode of ECLS. AKI, acute kidney injury; CRRT, continuous renal replacement therapy; ECLS, extracorporeal life support; CPB, cardiopulmonary bypass; VV, veno-venous; VA, veno-arterial; ECMO, extracorporeal membrane oxygenation; avg, average.

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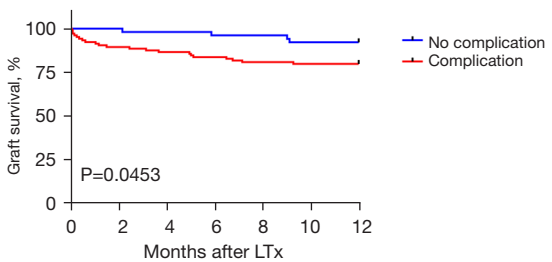
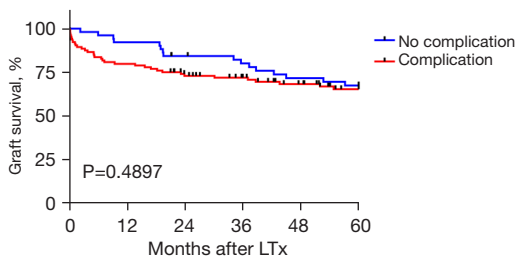
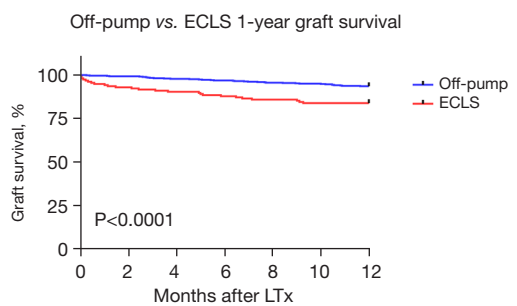


Number at risk	2 m	4 m	6 m	8 m	10 m	12 m
No complication	51	51	50	50	48	47
Complication	94	91	88	85	84	83

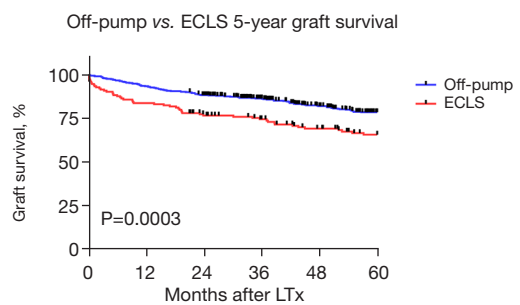


Number at risk	12 m	24 m	36 m	48 m	60 m
No complication	47	42	39	35	32
Complication	83	72	63	53	41

B



Number at risk	2 m	4 m	6 m	8 m	10 m	12 m
Off-pump	543	535	530	523	519	511
ECLS	145	141	137	134	131	130



Number at risk	12 m	24 m	36 m	48 m	60 m
Off-pump	511	477	416	361	309
ECLS	130	113	101	87	73

Figure 5 Survival analysis. (A) One- and 5-year survival of ECLS cases that did and did not develop ECLS-related complication. (B) One- and 5-year survival of off-pump and ECLS cases. ECLS, extracorporeal life support; LTx, lung transplantation; m, month; off-pump, transplantation performed without any ECLS.

Table 5 Other recent studies describing ECLS complications in LTx: study characteristics, patient inclusion

Study	Years	Number LTx	Number ECLS [%]	Pre-op. ECLS	Intra-op. ECLS	Post-op. ECLS	CPB	VA ECMO	VV ECMO	Central Can.	Peripheral Can.	Redo-LTx	SLTx
Orlitová *et al.*	2010–2020	703	156 [22]	√	√	√	√	√	√	√	√	√	√
Hoetzenecker *et al.* (8)	2010–2016	582	466 [80]	N/A	√	√	N/A	√	N/A	√	√	N/A	N/A
Ius *et al.* (14)	2010–2019	1,161	311 [27]	√	√	√	N/A	√	√	√	√	√	√
Halpern *et al.* (20)	2017–2021	237	68 [29]	√	√	√	N/A	√	N/A	√	N/A	√	N/A

√ = included in the study. ECLS, extracorporeal life support; LTx, lung transplantation; Pre-op., pre-operative; Intra-op., intra-operative; Post-op., post-operative; CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; VA, veno-arterial; VV, veno-venous; ECMO, extracorporeal membrane oxygenation; Can., cannulation; Redo-LTx, redo-LTx; SLTx, single lung transplantation; N/A, not available/excluded from the study.

Table 6 Other recent studies describing ECLS complications in LTx: type of complications & PGD-3 rates

Study	Revision hemoth.	AKI	Thromboembolism	Vascular	Wound Can. site	Mechanical	Neurological	PGD-3 0 h	PGD-3 24 h	PGD-3 48 h	PGD-3 72 h
Orlitová *et al.*	39/156 [25.0]	30/156 [19.2]	22/156 [14.1]	11/156 [7.1]	10/156 [6.4]	9/156 [5.8]	3/156 [1.9]	46/156 [29.5]	40/156 [25.6]	38/156 [24.4]	35/156 [22.4]
Hoetzenecker *et al.* (8)	41/466 [8.8]	40/466 [8.6]	13/466 [2.8]	9/466 [1.9]	N/A	N/A	2/466 [0.4]	N/A	N/A	N/A	22/466 [4.7]†
Ius *et al.* (14)	58/311 [18.6]	71/311 [22.8]	2/311 [0.6]	27/311 [8.7]	3/311 [1.0]	N/A	5/311 [1.6]	N/A	47/311 [15.1]	48/311 [15.4]	46/311 [14.8]
Halpern *et al.* (20)	15/68 [22.1]	6/68 [8.8]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	28 [16.6]†	

Values expressed as N [%]. †, calculated/estimated from data available in the manuscript; ‡, PGD-3 at 48 or 72 hours. See *Table 1* for definition of complication categories. ECLS, extracorporeal life support; LTx, lung transplantation; PGD-3, primary graft dysfunction grade 3; Revision hemoth., revision for hemothorax; AKI, acute kidney injury; N/A, not available.

CPB. Two centers also included redo-LTx (14,20). Most frequent complications (*Table 6*) in all studies were revision for hemothorax and acute kidney injury, ranging from 8.8–25% and 8.6-22.8%, respectively. PGD-3 at 72 hours ranged from 1.3–22%.

When analyzing pooled data of the three other studies (*Table 7*), our ECLS series includes the largest proportion of pre-operatively intubated patients (14.1% *vs.* 4.9%, P=0.0001) and the smallest proportion of lobar-LTx (6.4% *vs.* 13.4%; P=0.0161).

Comparing the indications for LTx, it can be noticed from reported series that Hoetzenecker *et al.* included more chronic obstructive pulmonary disease (COPD) (18.6% *vs.* 27.3%; P=0.0329) and Halpern *et al.* significantly more PF patients (38.5% *vs.* 76.5%; P<0.0001). Ius *et al.* included proportionally less COPD (18.6% *vs.* 4.5%; P<0.0001) and more PAH patients (9.6% *vs.* 23.2%; P=0.0004).

Discussion

This retrospective analysis of 156 ECLS SSLTx patients resulted in an overall ECLS-related complication rate of 67%. Previous studies on ECLS-related complications, reported a lower incidence or described only specific complications. Hoetzenecker *et al.* reported, in an intra-operative ECMO cohort of 159 patients, on 3.8% of directly ECLS-related complications and 40.4% of other complications (15).

The relatively higher incidence of complications in our series could be related to the detailed description of both directly and indirectly ECLS-related complications as well as the inclusion of CPB. Another important factor is that ECLS in our center is reserved for higher risk patients (e.g., PAH, bridged to LTx, etc.) or patients with intra-operative surgical complications. Interestingly, we observed that patients with ECLS-related complications experienced a decreased 1-year survival when compared to patients

Table 7 Other recent studies describing ECLS complications in LTx: comparison of demographic data

Parameters	Study 1: Orlitová *et al.* (n=156)	Study 2: Hoetzenecker *et al.* (n=466)	Study 3: Ius *et al.* (n=311)	Study 4: Halpern *et al.* (n=68)	Pooled data: study 2–4 (n=845)	P value			
						Study 1 *vs.* 2	Study 1 *vs.* 3	Study 1 *vs.* 4	Study 1 *vs.* 2–4
Age (years)	52 [36–59]	(40.4–45.2)±(15.3–16.2)†	49 [30–57]	64 [49–68]	N/A	N/A	N/A	N/A	N/A
BMI (kg/m^2)	24.5 [22.8–26.3]	22±4–9†	22.1 [18.4–26]	23.5 [21.1–27.6]	N/A	N/A	N/A	N/A	N/A
Female sex	78 [50.0]	238 [51.1]†	169 [54.3]	30 [44.1]	437 [51.7]	0.8534	0.3786	0.4683	0.7276
Pre-intub.	22 [14.1]	13 [2.8]†	28 [9.0]	N/A	41 [4.9]	<0.0001	0.1121	N/A	0.0001
Pre-bridge	25 [16.0]	N/A	79 [25.4]	1 [1.5]	80 [9.5]	N/A	0.0248	0.0011	0.0219
LTx indication									
COPD	29 [18.6]	127 [27.3]	14 [4.5]	12 [17.6]	153 [18.1]	0.0329	<0.0001	>0.9999	0.9101
ILD/PF	60 [38.5]	129 [27.7]	128 [41.2]	52 [76.5]	309 [36.6]	0.0156	0.6174	<0.0001	0.0647
CF	26 [16.7]	104 [22.3]	51 [16.4]	4 [5.9]	159 [18.8]	0.1407	>0.9999	0.0326	0.5757
PAH	15 [9.6]	47 [10.1]	72 [23.2]	N/A	119 [14.1]	>0.9999	0.0004	N/A	0.1587
Redo	14 [9.0]	N/A	17 [5.5]	9 [13.2]	26 [3.1]	N/A	0.1693	0.3450	0.0026
LTx type									
SSLTx	142 [91.0]	385 [82.6]‡	298 [95.8]	68 [100]	751 [88.9]	0.0102	0.0562	0.0066	0.4846
SLTx	4 [2.6]	N/A	13 [4.2]	N/A	13 [1.5]	N/A	0.4443	N/A	0.3211
Lobar-LTx	10 [6.4]	81 [17.4]	32 [10.3]	N/A	113 [13.4]	0.0006	0.2293	N/A	0.0161

Values expressed as median [IQR], mean (± SD) or n [%] according to the design of each study. †, calculated/estimated from data available in the manuscript; ‡, 182 (39%) of lungs underwent size reductio. ECLS, extracorporeal life support; LTx, lung transplantation; BMI, body mass index; Pre-intub., pre-operative intubation; Pre-bridge, pre-operative bridge; COPD, chronic obstructive pulmonary disease or obstructive lung disease; ILD, interstitial lung disease; PF, pulmonary fibrosis; CF, cystic fibrosis; PAH, pulmonary arterial hypertension or other pulmonary vascular disease; Redo, redo LTx; SSLTx, sequential single-lung transplantation; SLTx, single LTx; N/A, data not available; IQR, interquartile range; SD, standard deviation.

not developing any complication. However, this effect disappeared at 5-year follow-up time.

Main complications in our ECLS cohort were revision for hemothorax and acute kidney injury which is in accordance with observations described by Ius *et al.* (n=311) and Halpern *et al.* (n=68) (14,20). Furthermore, an association between severe post-operative bleeding in LTx patients and pre- and post-operative ECMO use was previously described by Adelmann *et al.* (35). In a study focusing on bridged patients only, Kim *et al.* reported an overall complication incidence of 56% in 100 patients, mostly related to bleeding (36).

Intra-operative use of ECLS during LTx depends on local practices and ranges from 27–100% in different large-volume LTx centers (14-16). Our reported data confirm that a majority (78% in our cohort) of LTx procedures can be performed without ECLS, thereby preventing any potential ECLS-related risks (37). On the other hand, routine ECLS offers intra-operative hemodynamic and respiratory stability with controlled reperfusion of the transplanted lung and decreased right ventricular strain as a counterweight to the risk of ECLS-related complications (38-41). Therefore, comparing LTx outcomes between centers using either of these strategies should be done with caution as recipient demographics and local ECLS practices may substantially differ, as shown in *Table* 7 (42).

Off-pump LTx strategy requires not only proper hemodynamic and respiratory management with intra-operative re-assessment of ECLS need, but also a meticulous surgical approach (43). As previously reported by our group, it is feasible and safe to use this strategy even in patients undergoing re-transplantation (44). However, it remains essential to identify upfront patients that may strongly benefit from ECLS, such as PAH or patients with severe pulmonary hypertension related to their respiratory condition (9). Our results demonstrate that indeed not all patients have the same baseline need for intra-operative ECLS. In contrast to 94% of PAH patients where ECLS was initiated, it was only required in 8% of COPD patients.

Efforts have been made to predict the need for

unplanned intra-operative ECLS use based on recipient-related characteristics (45). In our experience, hemodynamic and respiratory response following test-clamping prior to lung extraction is a reliable assessment tool in predicting ECLS use. Reported data in this study demonstrate that in the majority of ECLS cases, the decision to initiate ECLS was made when clamping was still reversible. This enables ECLS initiation in a non-acute setting and promotes a patient-tailored approach. Only in 12 cases intra-operative ECLS was initiated during lung implantation when reversing of test clamping was not possible anymore. Half of these patients needed ECLS due to surgical complications and the other half due to hemodynamic or respiratory deterioration.

Analysis of complications revealed that more complications occurred when VV-ECMO was used compared to VA-ECMO, which is not in accordance with current literature (28). However, it was also demonstrated that in our cases, peripheral cannulation was predominantly used for VV-ECMO, which might explain the highest chance for developing a cannulation site-related complication. Furthermore, the duration of support might play a role since VV-ECMO was used mainly as a bridge to LTx (median duration of 7 days), whereas VA-ECMO was mainly used for intra-operative support with a median duration of only 302 minutes.

It is well known that ECLS devices are a source of blood trauma and inflammatory activation that compromises the coagulation cascade (46). The complexity of the balance between bleeding and thrombo-embolisation when using ECLS is also reflected in our study. It remains a challenge despite implementing strategies to overcome this, like advances in ECLS technology or close monitoring of coagulation cascade using rotational thrombo-elastometry (47,48). Reported data in this study showed that 19% of ECLS patients required CRRT. Although the cause of kidney failure in these LTx patients is multifactorial, including pre-transplant presence of chronic kidney disease and intra-operative hemodynamic instability, also mechanisms of kidney injury associated with ECLS have been described (33,34).

A major topic of debate remains the association between ECLS and PGD. While Hoetzenecker and colleagues relate a low PGD incidence to standard VA-ECMO use, Loor and colleagues recently published a multicenter international registry showing an association between PGD and VA-ECMO (15,16). Furthermore, a recent single-center prospective observational study showed that levels of post-operative circulating cytokines were significantly higher in ECLS group compared to off-pump group and associated with endothelial cell dysfunction and PGD (49). On the other hand, another recent single-center retrospective study reports on lower leukocyte margination in post-reperfusion biopsies in ECMO group compared to off-pump (50). In our ECLS-series the incidence of PGD-3 within 72 hours was 47% which is higher than the 30.2% previously reported by our center for our overall SSLTx experience (51). This is most probably influenced by our ECLS strategy: either because ECLS could provoke PGD in some cases or because not starting ECLS at the beginning of the procedure might cause fluid accumulation in the transplanted lung resulting in urgent ECLS need during the procedure in some cases. This off-pump strategy might also result in selection of complex cases in the ECLS cohort which is reflected in the finding of the survival analysis between the ECLS and off-pump cohort.

Further prospective and randomized studies are needed to reach more evidence-based consensus on the preferred ECLS strategy for LTx patients. This will also allow to elucidate the role of ECLS in the development of PGD.

Limitations

The main limitation of this study is its retrospective nature that did not allow data collection in a controlled way. Post-operative bleeding leading to hemothorax requiring revision was the most common complication, however, we were unable to retrospectively collect data about the administered blood products as this was not available for the whole study period. Detailed data on renal function were not available. Our study is also limited by the purely descriptive analysis as our ECLS strategy does not allow for comparison or propensity score matching between ECLS and off-pump groups to exclude patient selection bias. The number of patients included in this study is limited by the nature of the off-pump LTx strategy used at our center. Lastly, the generalizability of our results is limited as ECLS practices and demographics of LTx recipients differ substantially among various large volume centers.

Conclusions

Although ECLS remains an essential part of any LTx program, its use is associated with complications that should be considered during the decision process. Larger databases could help to analyze complications and develop better strategies to tailor ECLS to specific patient characteristics and prevent ECLS-related complications in LTx. Further

prospective studies are needed to achieve an international consensus on the ECLS use during LTx.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). There is no experiment in this paper as it is a retrospective study of clinical strategies, therefore informed consent is not required. The study was approved by the local Ethics committee (No. S64384/S51577).

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